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Efficacy of Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers in the Management of Left Ventricular Systolic Dysfunction According to Race, Gender, and Diabetic Status

A Meta-Analysis of Major Clinical Trials

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OBJECTIVES This study sought to assess the effect of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers on all-cause mortality in patients with left ventricular (LV) systolic dysfunction according to gender, race, and the presence of diabetes.

BACKGROUND Major randomized clinical trials have established that ACE inhibitors and beta-blockers have life-saving benefits in patients with LV systolic dysfunction. Most patients enrolled in these trials were Caucasian men. Whether an equal effect is achieved in women, non-Caucasians, and patients with major comorbidities has not been established.

METHODS The authors performed a meta-analysis of published and individual patient data from the 12 largest randomized clinical trials of ACE inhibitors and beta-blockers to produce random effects estimates of mortality for subgroups.

RESULTS Data support beneficial reductions in all-cause mortality for the use of beta-blockers in men and women, the use of ACE inhibitors and some beta-blockers in black and white patients, and the use of ACE inhibitors and beta-blockers in patients with or without diabetes. Women with symptomatic LV systolic dysfunction probably benefit from ACE inhibitors, but women with asymptomatic LV systolic dysfunction may not have reduced mortality when treated with ACE inhibitors (pooled relative risk = 0.96; 95% confidence interval: 0.75 to 1.22). The pooled estimate of three beta-blocker studies supports a beneficial effect in black patients with heart failure, but one study assessing bucindolol reported a nonsignificant increase in mortality.

CONCLUSIONS Angiotensin-converting enzyme inhibitors and beta-blockers provide life-saving benefits in most of the subpopulations assessed. Women with asymptomatic LV systolic dysfunction may not achieve a mortality benefit when treated with ACE inhibitors. (J Am Coll Cardiol 2003;41:1529–38) © 2003 by the American College of Cardiology Foundation

Heart failure (HF) is a common medical condition that has a significant impact on public health. In the U.S., an estimated 4.8 million individuals are affected by HF, and 400,000 to 700,000 new cases develop each year (1). Heart failure is associated with substantial morbidity and mortality; it is a primary or secondary cause of death for approximately 250,000 people per year in the U.S. (2). According to the 2002 Heart and Stroke Statistical Update (2), HF was

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AIRE = Acute Infarction Ramipril Efficacy
BEST = Beta-blocker Evaluation of Survival Trial
CI = confidence interval
CIBIS = Cardiac Insufficiency Bisoprolol Study
CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study
COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Study
HF = heart failure
HR = hazard ratio
LV = left ventricular
MERIT-HF = Metoprolol Extended-release Randomized Intervention Trial in Heart Failure
RR = relative risk
RRR = ratio of relative risks
SAVE = Survival And Ventricular Enlargement
SMILE = Survival of Myocardial Infarction Long-term Evaluation
SOLVD = Studies Of Left Ventricular Dysfunction
TRACE = Trandolapril Cardiac Evaluation

the first-listed diagnosis for 962,000 hospitalizations in 1999, and it is the most common diagnosis among hospital patients age 65 years and older.

A series of randomized clinical trials have established that angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic blocking agents (also called beta-blockers) provide life-saving benefits in patients with HF or left ventricular (LV) systolic dysfunction. However, most of the patients enrolled in such studies have been Caucasian males. An important clinical question is whether the mortality benefit reported in these clinical trials is also achieved for other subpopulations, including women, non-Caucasians, and patients with selected comorbidities, such as diabetes mellitus.

There are several reasons to suspect that certain subpopulations might not experience the same benefits as white males. There is evidence that ACE inhibitors exert a lesser effect on blood pressure in black compared with nonblack hypertensive patients (3), and one of the ACE inhibitor trials reported a lesser effect of ACE inhibitors on reducing hospitalizations for black compared with nonblack patients (4). Similarly, men and women may respond differently to cardiac therapies. A preliminary analysis of one ACE inhibitor study suggested a trend toward lower mortality reduction in women compared with men (5). Because few of the randomized trials enrolled a sufficient number of women, blacks, or patients with comorbidities to have sufficient statistical power to support conclusions based on subgroup analyses, these important clinical questions are appropriate for meta-analysis.

Table 1. Sources of Data for Meta-Analysis From Principal Randomized Clinical Trials of ACE Inhibitors and Beta-Blockers

ACE Inhibitor Trial Name	Source of Data
AIRE (10)	Published data
CONSENSUS (8)	Individual patient data
SAVE (16,19)	Published data
SMILE (9)	Published data
SOLVD (21,28)	Individual patient data
TRACE (15)	Individual patient data
Beta-Blocker Trial Name	**Source of Data**
BEST (6,20,34)	Published data
CIBIS-II (7,12)	Published data
COPERNICUS (18)	Individual patient data
MERIT-HF (13,14,22)	Individual patient data
U.S. Carvedilol (17,23)	Published data

ACE = angiotensin-converting enzyme. Trial acronyms as in Abbreviation Box.

METHODS

We synthesized data from the 12 largest randomized trials of ACE inhibitors and beta-blockers to test the hypotheses of differences by gender, race, and comorbidities in reduction in all-cause mortality (Table 1) (6–24). Originally, we had planned to synthesize data from all randomized trials of these two drug classes that had at least 12 weeks duration of follow-up and that reported mortality outcomes (25). We performed an exhaustive literature search and identified 39 reports of randomized trials of ACE inhibitors and 35

Table 2. Effect of ACE Inhibitors on Mortality From Heart Failure in Male and Female Patients

				RR Analysis		
Study Name	Total N	Male N	Female N	RR Male (95% CI)	RR Female (95% CI)	RRR (95% CI)
CONSENSUS	253	179	74	0.61 (0.44–0.85)	1.14 (0.68–1.90)	1.86 (1.01–3.42)
SAVE	2,231	1,841	390	0.80 (0.68–0.95)	0.99 (0.67–1.47)	1.24 (0.80–1.90)
SMILE	1,556	1,128	428	0.61 (0.39–0.96)	0.74 (0.47–1.18)	1.22 (0.64–2.32)
SOLVD-Prevention	4,228	3,752	476	0.90 (0.77–1.05)	1.15 (0.74–1.78)	1.27 (0.80–2.02)
SOLVD-Treatment	2,569	2,065	504	0.89 (0.80–0.99)	0.86 (0.67–1.09)	0.97 (0.74–1.26)
TRACE	1,749	1,248	501	0.79 (0.68–0.91)	0.90 (0.74–1.11)	1.15 (0.90–1.48)
Random effects pooled estimate		10,213	2,373	0.82 (0.74–0.90)	0.92 (0.81–1.04)	1.15 (0.99–1.33)

ACE = angiotensin-converting enzyme; CI = confidence interval; RR = relative risk; RRR = ratio of relative risk. Trial acronyms as in Abbreviation Box.

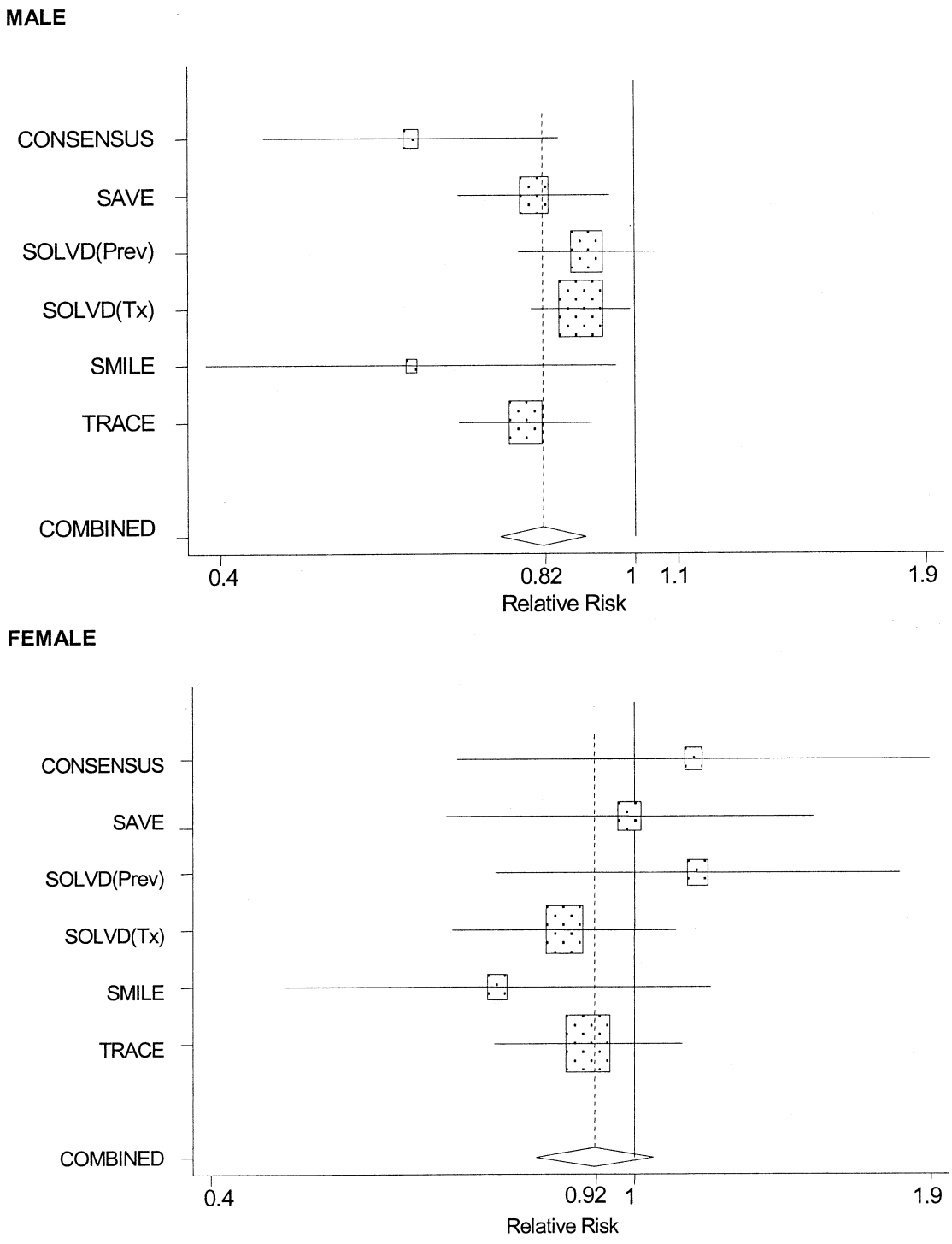

Figure 1. Effect of angiotensin-converting enzyme inhibitors on mortality in patients with heart failure. For each study, the **size of the box** is proportional to the sample size, and the **lines** denote the 95% confidence interval. For the combined result, the **ends of the diamond shape** denote the 95% confidence interval. Trial acronyms defined in the Abbreviation Box. Prev = prevention; Tx = treatment.

reports of randomized trials of beta-blockers that reported mortality outcomes and were of at least 12 weeks' duration. However, few studies published mortality outcomes stratified by our subpopulations of interest, and data for most of the smaller trials were not made available through contacts with the study investigators. Therefore, we elected to seek more intensive subpopulation data from the 12 largest studies (Table 1). We calculated that the seven largest ACE inhibitor studies (18 reports) enrolled 14,572 patients (83% of total), whereas the remaining 19 ACE inhibitor trials (21 reports) enrolled an aggregate of 3,033 patients (17% of total). Similarly, the five largest beta-blocker studies (15 reports) enrolled 12,727 patients (81% of total), whereas the remaining 19 beta-blocker studies (20 reports) enrolled

Table 3. Effect of ACE Inhibitors on Mortality From Heart Failure in Male and Female Patients Reported Separately for Prevention Studies and Treatment Studies

Analysis	RR Male (95% CI)	RR Female (95% CI)	RRR (95% CI)
Treatment (symptomatic) studies	0.80 (0.68–0.93)	0.90 (0.78–1.05)	1.15 (0.88–1.51)
Prevention (asymptomatic) studies	0.83 (0.71–0.96)	0.96 (0.75–1.22)	1.25 (0.94–1.65)

Abbreviations as in Table 2.

2,938 patients (19% of total). Therefore, most of the statistical power to detect differences in subpopulations resided in the few largest studies. By extracting published data on subpopulations and by obtaining individual patient data either from the original investigators or through the Food and Drug Administration, we obtained a nearly complete dataset for our meta-analysis.

Meta-analysis. The principal questions for meta-analysis were as follows: 1) What are the associations between treatment (ACE inhibitors or beta-blockers) and all-cause mortality for male and female patients, patients with or without diabetes, and black and white patients with HF? 2) Do these associations vary (e.g., are there statistically significant differences) by gender (female vs. male), diabetes status (those with diabetes vs. those without), and race (black vs. white patients)?

All reports that presented the relevant patient subpopulation data did so in the form of two-by-two tables of all-cause mortality by treatment group for each subpopulation. Alternatively, if we were given the patient-level data, we preferred to construct this table directly.

To answer our first question of interest, for each subpopulation (e.g., women), we estimated the log mortality relative risk (RR), which is equal to the log of the risk of dying for women who received ACE inhibitors divided by the risk of dying for women who received placebo. The standard error for the log RR was also estimated, and a 95% confidence interval (CI) was constructed. We then back-transformed to the unlogged scale for interpretability so that our final statistic for each subpopulation in each study was the RR with its associated CI. For subpopulations for which we had data from at least three studies, we combined data across studies using a random effects model (26).

To answer our second question, that is, whether the

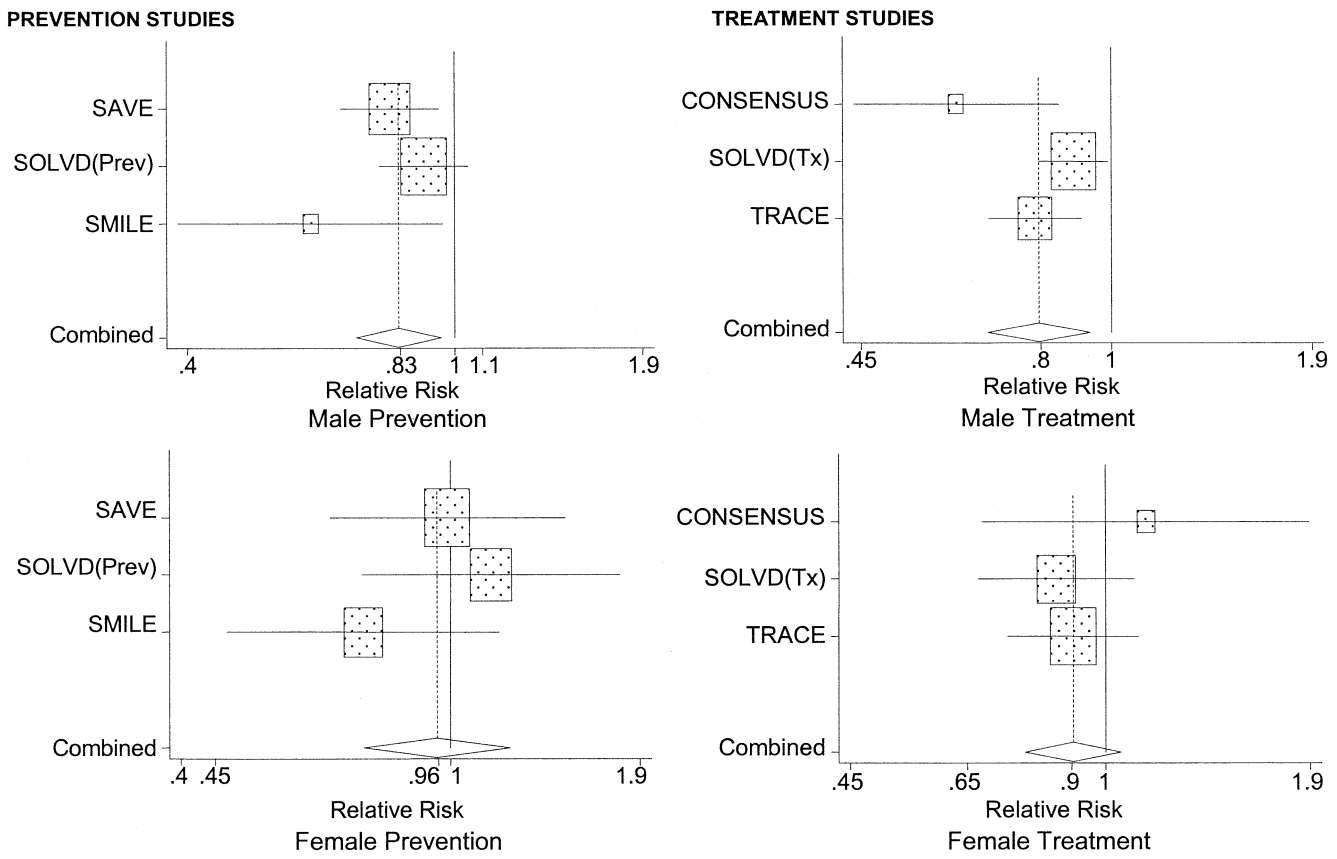

Figure 2. Effect of angiotensin-converting enzyme inhibitors on mortality in male and female patients with heart failure (random effects pooled estimate). For each study, the **size of the box** is proportional to the sample size, and the **lines** denote the 95% confidence interval. For the combined result, the **ends of the diamond shape** denote the 95% confidence interval. Trial acronyms defined in Abbreviation Box.

Table 4. Effect of ACE Inhibitors on Mortality From Heart Failure in Diabetic and Nondiabetic Patients

		RR Analysis				
Study Name	Total N	Nondiabetic N	Diabetic N	RR, Nondiabetic (95% CI)	RR, Diabetic (95% CI)	RRR (95% CI)
CONSENSUS	253	197	56	0.64 (0.46–0.88)	1.06 (0.65–1.74)	1.67 (0.93–3.01)
SAVE	2,231	1,739	492	0.82 (0.68–0.99)	0.89 (0.68–1.16)	1.09 (0.79–1.50)
SMILE	1,556	1,253	303	0.79 (0.54–1.15)	0.44 (0.22–0.87)	0.56 (0.25–1.22)
SOLVD-Prevention	4,228	3,581	647	0.97 (0.83–1.15)	0.75 (0.55–1.02)	0.77 (0.54–1.09)
SOLVD-Treatment	2,569	1,906	663	0.84 (0.74–0.95)	1.01 (0.85–1.21)	1.21 (0.97–1.50)
TRACE	1,749	1,512	237	0.85 (0.74–0.97)	0.73 (0.57–0.94)	0.87 (0.65–1.15)
Random effects pooled estimate		10,188	2,398	0.85 (0.78–0.92)	0.84 (0.70–1.00)	1.00 (0.80–1.25)

Abbreviations as in Table 2. Trial acronyms as in Abbreviation Box.

association differed between subpopulations (e.g., female vs. male), we determined whether statistical differences existed between the RRs for related subpopulations. To do this, a test statistic equal to the ratio of relative risks (RRR) (which equals the female RR divided by the male RR, patients with diabetes RR divided by those without diabetes RR, or black RR divided by white RR) was constructed. If this test statistic differed significantly from one, then we inferred that the two subgroup RRs are significantly different. As before, we performed the analysis on the log scale, and we then back-transformed the estimate and its CI to the unlogged scale so that our final test statistic for each study was the RRR. As before, we combined data across studies to produce a pooled RRR. We tested whether this pooled RRR was significantly different from one, which would indicate a significant association between treatment effect and subpopulation.

Because follow-up times varied across studies and calculating RR does not take this variation (or the censoring of observations) into account, we also assessed the mortality associated with ACE inhibitors and beta-blockers, respectively, on the hazard ratio scale. The majority of our studies presented hazard ratios (HRs) and CIs, and after transforming these statistics to the log scale, we extracted the log HR and its standard error for each study and subpopulation of interest. We followed the same analytic strategy for the HR as for the RR, conducting a random effects pooled analysis to produce a pooled HR across studies. We then constructed a pooled ratio of HRs to compare the HRs in each subpopulation. Hazard ratio results are presented when they differed from the RR results.

For each drug and patient subpopulation comparison, we assessed the possibility of publication bias by evaluating funnel plots of the individual study log RRs and HRs, respectively, and an adjusted correlation test (27) and a regression asymmetry test (28). We found no evidence of publication bias in any of the study subpopulations assessed. In addition, we performed a sensitivity analysis, as studies varied in their definitions of racial groups. For racial comparisons, if the study provided data separately by racial subgroup, we utilized these data. If data were not stratified in that way, we used data for black versus nonblack patients. Our last choice was data for nonwhite versus white patients. The results of this sensitivity analysis did not differ markedly from the primary conclusions.

RESULTS

ACE inhibitors. GENDER. We were able to obtain gender-stratified data for all seven major studies to calculate the effect of ACE inhibitors on mortality. The seven studies were Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), Survival And Ventricular Enlargement (SAVE), Studies Of Left Ventricular Dysfunction (SOLVD) Prevention, SOLVD Treatment, Survival of Myocardial Infarction Long-term Evaluation (SMILE), Trandolapril Cardiac Evaluation (TRACE), and Acute Infarction Ramipril Efficacy (AIRE). In aggregate, these studies included 2,898 women and 11,674 men and lasted as few as six months (CONSENSUS) to as many as 42 months (SAVE). The pooled random effects estimates from the six studies with RR data yielded values for men of 0.82 (95% CI: 0.74 to 0.90) and for women of 0.92 (95% CI: 0.81 to 1.04). These results are displayed in Table 2 and Figure 1. The corresponding pooled random effects estimates from the six studies with HR data yielded values for men of 0.76 (95% CI: 0.66, 0.87) and for women of 0.84 (95% CI: 0.72, 0.98). The difference in effect between men and women approached statistical significance for the RRR ($p = 0.07$).

Table 5. Effect of ACE Inhibitors on Mortality From Heart Failure in Black and White Patients

Study Name	Total N	White N	Non-White N	Black N	Non-Black N	RR White (95% CI)	RR Black (95% CI)	RRR (95% CI)
SAVE	2,231	1,993	238			0.84 (0.71–0.99)	0.78 (0.50–1.21)	1.08 (0.67–1.73)
SOLVD-Prevention	4,228	3,657	571	404	3,824	0.95 (0.81–1.12)	0.87 (0.60–1.25)	0.91 (0.61–1.36)
SOLVD-Treatment	2,569	2,061	508	396	2,173	0.89 (0.79–1.00)	0.93 (0.74–1.17)	1.04 (0.81–1.35)
Random effects pooled estimate		7,711	1,317	800	5,997	0.89 (0.82–0.97)	0.89 (0.74–1.06)	1.01 (0.83–1.24)

Abbreviations as in Table 2. Trial acronyms as in Abbreviation Box.

Table 6. Effect of Beta-Blockers on Mortality From Heart Failure in Male and Female Patients

				RR Analysis		
Study-Name	Total N	Male N	Female N	RR Male (95% CI)	RR Female (95% CI)	RRR (95% CI)
CIBIS-II	2,647	2,132	515	0.71 (0.58–0.87)	0.52 (0.30–0.89)	0.73 (0.41–1.30)
COPERNICUS	2,287	1,822	465	0.68 (0.54–0.86)	0.63 (0.39–1.04)	0.93 (0.54–1.59)
MERIT-HF	3,991	3,093	898	0.63 (0.50–0.78)	0.93 (0.58–1.49)	1.49 (0.88–2.51)
U.S. Carvedilol HF	1,094	838	256	0.44 (0.24–0.82)	0.32 (0.11–0.93)	0.73 (0.21–2.51)
Random effects pooled estimate		7,885	2,134	0.66 (0.59–0.75)	0.63 (0.44–0.91)	0.99 (0.70–1.41)

Abbreviations as in Table 2. Trial acronyms as in Abbreviation Box.

In a post hoc subgroup analysis, studies were divided into those treating symptomatic HF (CONSENSUS, SOLVD Treatment, and TRACE) compared with those treating asymptomatic LV systolic dysfunction (SAVE, SOLVD Prevention, and SMILE). The pooled analysis included 1,079 women in the symptomatic HF studies and 1,294 women in the asymptomatic HF studies. Men clearly benefit when treated with ACE inhibitors for either symptomatic or asymptomatic LV systolic dysfunction. The evidence indicates that women with symptomatic HF probably benefit when treated with ACE inhibitors, although the benefit may be somewhat less than that seen in men (RR = 0.90; 95% CI: 0.78 to 1.05). A potential difference in efficacy of ACE inhibitors between men and women in the treatment of asymptomatic LV dysfunction was suggested. In the studies analyzed, a significant mortality benefit for women with asymptomatic LV dysfunction was not demonstrated (RR = 0.96; 95% CI: 0.75 to 1.22; Table 3 and Fig. 2). These results are compatible with an earlier preliminary analysis of the SOLVD data (5). However, the RRR between men and women does not reach statistical significance, so that a significant difference in response between men and women cannot be concluded.

DIABETES. Six studies stratified data by diagnosis of diabetes, permitting calculation of the differential effect of ACE inhibitors on mortality. These studies were CONSENSUS, SAVE, the two SOLVD studies, SMILE, and TRACE. In aggregate, these studies included 2,398 patients with diabetes and 10,188 patients without diabetes. All of these studies contributed data to our RRs analysis; however, the SAVE study did not contain data that we could use for our HRs analysis. Both analyses yielded similar results. The random effects pooled estimate of the RR of mortality in patients with diabetes is 0.84 (95% CI: 0.70 to 1.00), whereas the estimate of the RR in patients without diabetes is 0.85 (95% CI: 0.78 to 0.92). These data are presented in Table 4. We interpret these results as indicating that patients with diabetes as well as those without diabetes achieve reductions in mortality when treated with ACE inhibitors for HF.

RACE. Three studies provided data stratified by patient race to assess the effects of ACE inhibitors on mortality. The studies with appreciable numbers of black patients were SAVE and the two SOLVD studies. The remaining ACE inhibitor studies (AIRE, CONSENSUS, SMILE, and TRACE) were conducted primarily in Scandinavian and European countries and did not include substantial numbers of black patients. The SAVE study did not present data that allowed us to calculate the HRs, which left only two studies (the SOLVD studies), an insufficient number to pool for this analysis. Therefore, only a pooled RR analysis was performed, which yielded an estimate in white patients of 0.89 (95% CI: 0.82 to 0.97) and an estimate in black patients of 0.89 (95% CI: 0.74 to 1.06). These data are presented in Table 5. Whereas the RR reduction in black patients did not achieve conventional levels of statistical significance, the estimate of effect is the same as the statistically significant reduction seen in white patients. Furthermore, the two estimates of effect (for black and white patients) do not differ from each other statistically. The most likely explanation for the lack of statistical significance in the estimate for black patients is the much smaller sample size, which increases the standard error and 95% CIs. We interpret these data as indicating that there is no evidence that black patients achieve lesser or greater reductions in mortality than white patients when treated with ACE inhibitors for HF. These results are consistent with the analysis by the SOLVD Investigators that there was not a lesser reduction in mortality among black compared with white patients in the SOLVD studies, although these investigators did report a difference in hospitalization rates in black patients compared with white patients (29).

Table 7. Effect of Beta-Blockers on Mortality From Heart Failure in Diabetic and Nondiabetic Patients

Study Name	Total N	Nondiabetic N	Diabetic N	RR, Nondiabetic (95% CI)	RR, Diabetic (95% CI)	RRR (95% CI)
CIBIS-II	2,647	2,335	312	0.66 (0.54–0.81)	0.81 (0.52–1.27)	1.23 (0.75–2.02)
COPERNICUS	2,287	1,701	586	0.67 (0.52–0.85)	0.68 (0.47–1.00)	1.02 (0.65–1.61)
MERIT-HF	3,991	3,006	985	0.62 (0.48–0.79)	0.81 (0.57–1.15)	1.32 (0.86–2.02)
Random effects pooled estimate		7,042	1,883	0.65 (0.57–0.74)	0.77 (0.61–0.96)	1.19 (0.91–1.55)

Abbreviations as in Table 2. Trial acronyms as in Abbreviation Box.

Table 8. Effect of Beta-Blockers on Mortality From Heart Failure in Black and White Patients

	RR Analysis							
Study Name	Total N	White N	Non-White N	Black N	Non-Black N	RR White (95% CI)	RR Black (95% CI)	RRR (95% CI)
COPERNICUS	2,287	2,069	218	121	2,166	0.66 (0.53–0.82)	0.62 (0.19–2.01)	0.94 (0.28–3.11)
MERIT-HF	3,991	3,755	236	207	3,784	0.67 (0.54–0.82)	0.79 (0.36–1.76)	1.19 (0.52–2.70)
U.S. Carvedilol HF	1,094			217	877	0.38 (0.20–0.70)	0.53 (0.19–1.48)	1.41 (0.43–4.68)
BEST	2,708			627	2,081	0.85 (0.74–0.96)	1.17 (0.94–1.47)	1.39 (1.07–1.79)
Random effects pooled estimate (with BEST)		5,824	454	1,172	8,908	0.69 (0.55–0.85)	0.97 (0.68–1.37)	1.35 (1.07–1.71)
Random effects pooled estimate (without BEST)		5,824	454	545	6,827	0.63 (0.52–0.77)	0.67 (0.38–1.16)	1.17 (0.65–2.11)

Abbreviations as in Table 2. Trial acronyms as in Abbreviation Box.

Beta-blockers. GENDER. Five studies on the effects of beta-blocker treatment on mortality stratified data by gender. The studies were Cardiac Insufficiency Bisoprolol Study (CIBIS)-II, Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS), Metoprolol Extended-release Randomized Intervention Trial in Heart Failure (MERIT-HF), Beta-blocker Evaluation of Survival Trial (BEST), and U.S. Carvedilol. The CIBIS-II study contributed data only to the RR analysis. Bucindolol, which was the beta-blocker evaluated in BEST, was judged to be potentially different in action from the other beta-blockers. Therefore, pooled analyses were performed with and without the inclusion of BEST. The BEST study contributed data only to the HR analysis, which yielded a result similar to the RR analysis, and only the RR analysis is presented here. In aggregate, the pooled studies included 2,134 women and 7,885 men. Both analyses yielded similar results. The random effects pooled estimate for the RR of mortality for women was 0.63 (95% CI: 0.44 to 0.91), whereas for men, the estimate was 0.66 (95% CI: 0.59 to 0.75). The corresponding values for the HR analysis were 0.75 (95% CI: 0.51 to 1.09) for women and 0.68 (95% CI: 0.51 to 0.89) for men. These data are presented in Table 6. Our interpretation of these data is that women and men with symptomatic HF have reduced mortality when treated with beta-blockers.

DIABETES. Three studies stratified data by diagnosis of diabetes, permitting calculation of the differential effect of beta-blockers on mortality (CIBIS, COPERNICUS, MERIT-HF). In aggregate, these studies included 1,883 patients with diabetes and 7,042 patients without diabetes. The only pooled estimates that were possible were the RRs, which yielded a value of 0.65 (95% CI: 0.57, 0.74) for nondiabetic patients and a value of 0.77 (95% CI: 0.61, 0.96) for diabetic patients. This RRR was not statistically significant. These data are presented in Table 7. Our interpretation of these data is that patients with diabetes and HF have reduced mortality when treated with beta-blockers. It is possible that the relative reduction in mortality may be less for patients with diabetes than for those without diabetes, but because the absolute risk of mortality is greater in diabetic patients, the absolute risk reduction is almost certainly equal or greater for diabetic than for nondiabetic HF patients treated with beta-blockers.

RACE. We were able to obtain race-stratified data to assess the effects of beta-blocker treatment on mortality in four studies. These studies were BEST, COPERNICUS, MERIT-HF, and U.S. Carvedilol. As noted above, bucindolol was judged to be potentially clinically dissimilar to the beta-blockers; therefore, pooled analyses were done with and without the inclusion of BEST. The CIBIS-II study was conducted in Scandinavian and European countries and did not enroll appreciable numbers of black patients. In aggregate, the four studies included in the pooled analysis enrolled 1,172 black and more than 8,000 white patients. Both the RR analysis and the HR analysis yielded similar results. The pooled random effects estimate (including BEST) of the RR of the effect on mortality for black patients was 0.97 (95% CI: 0.68 to 1.37), whereas for white patients, it was 0.69 (95% CI: 0.55 to 0.85). The pooled random effects estimate (without BEST) of the RR of the effect on mortality for black patients was 0.67 (95% CI: 0.38 to 1.16). These data are displayed in Table 8 and Figure 3.

Our interpretation of these data is that black patients are likely to have the same RR reduction as white patients treated with the beta-blockers bisoprolol, metoprolol, or carvedilol. Although the results for black patients were not statistically significant compared with placebo, the point estimates of effect (without BEST) were similar to those in white patients; therefore, we judge that the smaller sample size is the most likely reason for this finding. In contrast, bucindolol was associated with worse mortality outcomes in black patients than in white patients, and is not effective in decreasing mortality in blacks.

DISCUSSION

For most of the subpopulations assessed in our meta-analysis, our results are reassuring in that we found evidence supporting beneficial reductions in all-cause mortality with the use of beta-blockers in men and women, the use of ACE inhibitors in black and white patients, and the use of either drug in patients with diabetes. However, we did find evidence that women with asymptomatic LV dysfunction

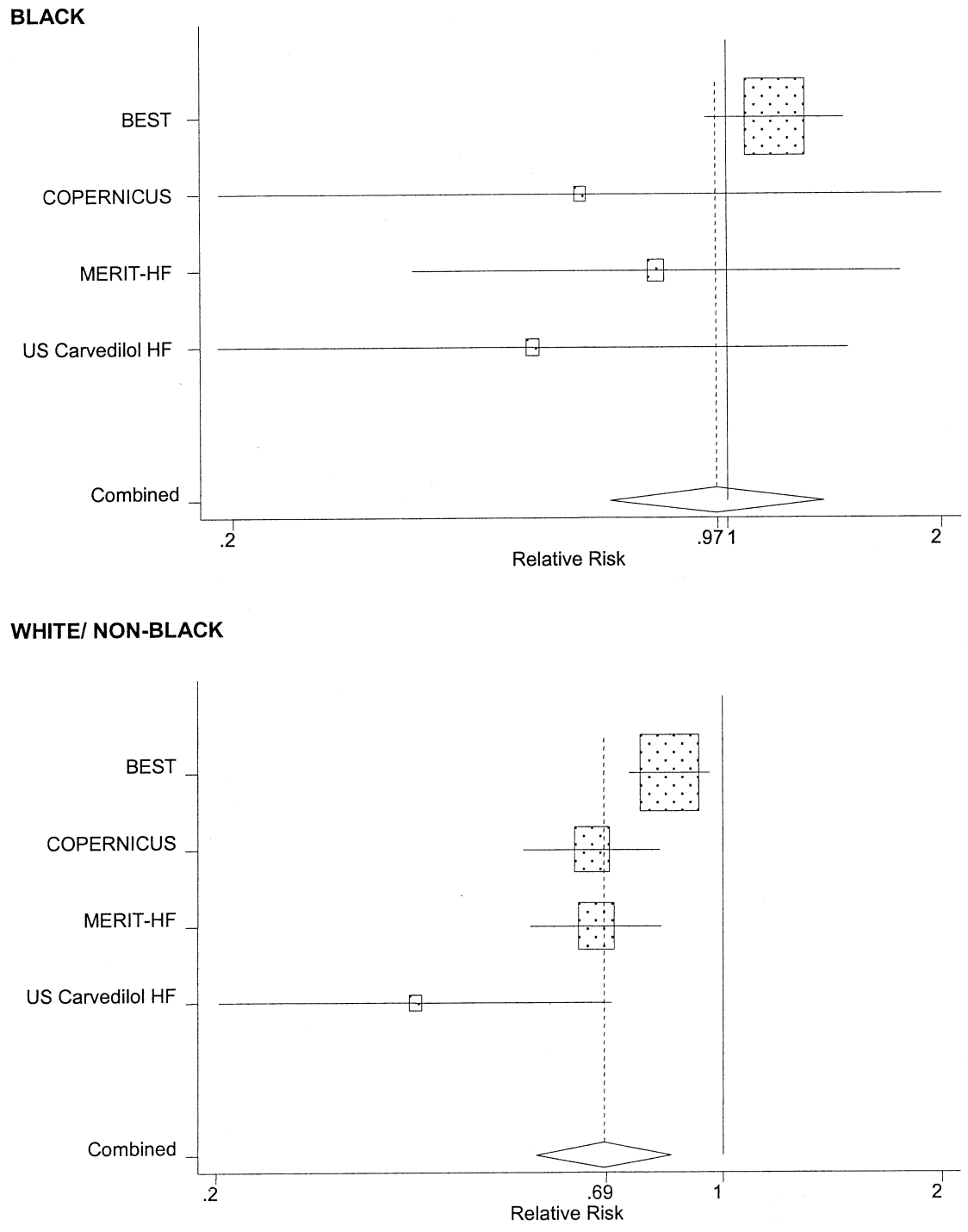

Figure 3. Effect of beta-blockers on mortality in patients with heart failure. For each study, the **size of the box** is proportional to the sample size, and the **lines** denote the 95% confidence interval. For the combined result, the **ends of the diamond shape** denote the 95% confidence interval. Trial acronyms defined in Abbreviation Box.

may not have reduced mortality when treated with ACE inhibitors, and additional study is needed to address this issue.

We also found evidence supporting the beneficial effect of beta-blocker use in black patients. For three of the beta-blocker studies, the pooled estimate of effect suggested that black patients and white patients have similar reductions in all-cause mortality when treated with beta-blockers. However, one study, which was unique in that it assessed the beta-blocker bucindolol, reported a statistically significant adverse effect on mortality in blacks relative to whites. This may be due in part to bucindolol's partial agonist activity (30), a property that has been associated with adverse outcomes in patients with prior myocardial infarction (31)

and in patients with HF (32). In any case, these results suggest that the benefits of beta-blockers cannot be considered equivalent across the entire class of available agents.

Study limitations. Our meta-analysis has several potential limitations common to most meta-analyses. We cannot adjust for inherent biases in the individual studies, and in some cases there was substantial between-study heterogeneity. The most important limitation specific to this analysis is the inability to control for possible differences between subpopulations in the etiology of HF. Women and blacks are less likely than white males to have an ischemic etiology of HF. In the SOLVD studies, for example, 27.7% of women had nonischemic HF, as compared with 16.1% of men ($p < 0.001$) (33). Similarly, 40.9% of blacks had nonischemic HF, as compared with only 14.6% of whites ($p < 0.001$) (33). It is possible that the benefits of ACE inhibitors in HF are due in part to a vasculoprotective effect, as suggested by the Heart Outcomes Prevention Evaluation (HOPE) study (34). Likewise, the benefits of beta-blockers may be due in part to their anti-ischemic effects. Further research is needed to answer these questions.

Our findings suggest several important future research studies. Additional data are needed to support or refute the evidence that different beta-blockers may have different effects on all-cause mortality in black patients. Future studies of existing or new beta-blocker drugs for HF need to include sufficient numbers of black patients to separately assess outcomes in this population, as a similar effect in black patients and white patients cannot be assumed.

A second area for future research is further assessment of the effect of ACE inhibitors in women with asymptomatic LV dysfunction. It may be possible to answer this question by a more complete analysis of existing data from randomized clinical trials. This would require an individual patient data meta-analysis, which in turn would require obtaining individual patient data from all of the randomized trials. Although such an effort would be costly, it would be substantially less expensive and more ethical than mounting a new clinical trial designed to answer this question. Until additional data become available, we do not consider our findings sufficient to warrant withholding ACE inhibitors from asymptomatic women with reduced LV systolic function.

Additionally, other outcomes of interest should be examined for all patient subpopulations, including cardiac mortality, symptoms, quality of life, and health care utilization. There is also a need to examine other major subpopulations, including the elderly and patients with impaired renal function. Individual patient level data from the major randomized clinical trials may be sufficient to answer these questions, but published data are scant.

If our findings of differential efficacy in selected subgroups are confirmed, then additional research aimed at identifying the cause for these disparities should be undertaken. As noted above, one possibility is that these findings do not represent differences in men or women or in black patients or white patients, but rather reflect differing efficacy of these drugs according to the cause of HF (e.g., ischemic or nonischemic), which may differ by gender or race. Alternatively, there could be a molecular basis for differences in response by gender and race.

Given the robust evidence of benefit for ACE inhibitors and beta-blockers in reducing mortality, future work should also focus on how to increase the use of these therapies by addressing potential barriers for practitioners and patients.

In summary, meta-analysis of the major randomized clinical trials of ACE inhibitors and beta-blockers in patients with HF and LV systolic dysfunction indicate that these agents reduce all-cause mortality in men, whites, diabetics, and nondiabetics. In addition, beta-blockers are effective in women, ACE inhibitors are effective in blacks, and, with the exception of bucindolol, beta-blockers are effective in blacks. Angiotensin-converting enzyme inhibitors are also effective in women with symptomatic HF, but the data are inconclusive on the value of ACE inhibitors in women with asymptomatic LV dysfunction. Although we do not recommend changes in present treatment guidelines, additional study is needed to evaluate the effects of ACE inhibitors in women with asymptomatic LV dysfunction and to determine the mechanisms underlying potential differential effects of these agents in diverse patient populations.

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